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INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

BEST AVAILABLE COPY

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.****900/Del/2003*** *dated* ***15th July 2003.***

Witness my hand this 13th day of August 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

Chemistry
C07D 305/08

0900 DEL 03

15 JUL 2003

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR PREPARATION OF OXETAN-2-ONES"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. MOHAN PRASAD

c. KESHAV DEO

d. ANAND PANDEY

e. KILOL PATEL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, YATENDRA KUMAR, MOHAN PRASAD, KESHAV DEO, ANAND PANDEY, KILOL PATEL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

b. (YATENDRA KUMAR)

c. (MOHAN PRASAD)

d. (KESHAV DEO)

e. (ANAND PANDEY)

(KILOL PATEL)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
- a. Complete Specification (3 copies)
- b. Drawings (3 copies)
- c. Priority document(s)
- d. Statement and Undertaking on FORM – 3
- e. Power of Authority (Not required)
- f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. 508496 dated : 27-6-2003 drawn on HDFC BANK LTD.

We request that a patent may be granted to us for the said invention.

Dated this 8TH day of **July, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

DEL 05
15 JUL 2003

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR PREPARATION OF OXETAN-2-ONES

PATENT OFFICE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Processes for the preparation of diastereomerically and enantiomerically pure oxetan-2-ones are provided. Further, processes for the preparation of enzyme inhibitors using the oxetan-2-ones are provided.

Oxetan-2-ones of formula I, as shown in the accompanied drawings, wherein R^1 is undecyl or 2Z,5Z-undecadienyl are known from US 4202824. These oxetan-2-ones are useful intermediates for the preparation of lipstatin, tetrahydrolipstatin, esterastin, tetrahydroesterastin, and structurally related compounds which are useful as pancreatic lipase-inhibiting agents, for the prevention and treatment of obesity and hyperlipaemia.

Several processes have been reported for the preparation of oxetan-2-ones of formula I, such as in US 4202824; US 4983746; *J. Org. Chem.* 1988, 53, 1218-1221; *Tetrahedron Lett.* 1990, 31, 3645-3648; *SYNLETT*, 1991, 11, 781-782; *J. Org. Chem.* 1991, 56, 4714-4718; *J. Org. Chem.* 1993, 58, 7768-7781; and *J. Chem. Soc., Perkin Trans. 1,* 1998, 17, 2679-2686. The synthesis of (3S,4S)-3-hexyl-4-(2S)-2-hydroxytridecyloxetan-2-one from tandem aldol-lactonization of (R)-3-(2-methoxyprop-2-oxy)tetradecanal and lithium enolate of 1-octanoylbenzotriazole has been reported in *J. Org. Chem.* 1999, 64, 5301-5303 and US 5902886. The above processes require multiple steps, unstable intermediates, or complicated stereomeric purification processes such as chromatography and therefore inevitably lead to poor yields or purity.

The preparation of the corresponding (R)-hydroxy isomer viz., (3S,4S)-3-hexyl-4-(2R)-2-hydroxytridecyloxetan-2-one from (R)-3-(tert-butyldimethylsilyloxy)tetradecanal and 3-hexyl-3-trimethylsilylketen has been described, for example, in *Synthesis*, 1994, 1294-1300.

In one aspect, a process for preparing oxetan-2-one of formula I, as shown in the accompanied drawings, wherein R^1 is undecyl or 2Z, 5Z-undecadienyl comprising:

a. reacting an aldehyde of formula II, as shown in the accompanied drawings, wherein R^1 is undecyl or 2Z,5Z-undecadienyl, with a metal enolate of formula III, as shown in the accompanied drawings, wherein R^2 is selected from the group consisting of fluorine, substituted or unsubstituted aryloxy, arylsulfanyl, and heteroaryl groups, and M is selected from the group of mono-, di-, tri-, and tetravalent metal containing groups;

b. hydrolyzing the resulting diastereomeric mixture of trans-oxetan-2-ones of formula IV, as shown in the accompanied drawings, wherein R^1 is as defined above; and

c. separating the diastereomerically pure oxetan-2-ones of formula I by crystallization.

The oxetan-2-one of formula I can be converted to a compound of formula V, as shown in the accompanied drawings, wherein R^1 is undecyl or 2Z,5Z-undecadienyl; R^3 is isobutyl or carbamoylmethyl ; and R^4 is formyl or acetyl by methods known in the art.

In another aspect, a process for preparing a compound of formula V is provided, which comprises treating the oxetan-2-one of formula I directly with an acid of formula VI, as shown in the accompanied drawings, wherein R^5 is an amino protecting group and R^3 is as defined above, and dicyclohexylcarbodiimide; followed by cleaving off the amino protecting group R^5 of the obtained ester of formula VIII, as shown in the accompanied drawings, wherein R^1, R^3 and R^5 are as defined above; and reacting with an alkanoylating agent to introduce the group R^4 to obtain the compound of formula V.

The aryl part of the aryloxy and arylsulfonyl groups, as used herein, includes any aromatic mono- or polycyclic ring system, such as benzene, and naphthalene. The heteroaryl group includes mono- or polycyclic heteroaromatic ring systems, such as pyridine and furan.

Examples of R^2 include phenoxy or 1-benzotriazolyl. Examples of M include Li, MgBr, ZnCl and $Ti(Oalkyl)_3$.

The reaction of the aldehyde of formula II with the metal enolate of formula III may be performed in a suitable solvent. Suitable solvents for the reaction are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include ethers, such as diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran (THF).

In general, the reaction may be carried out at a temperature range from about -20°C to about -70°C, for example at a temperature range from about -100°C to about -80°C.

The reaction can be quenched by an acid such as hydrochloric acid, or a salt solution such as ammonium chloride solution and the diastereomeric mixture (SSS and SRR) of trans-oxetan-2-ones of formula IV can be recovered by extraction followed by crystallization.

Lithium enolates of the formula III (M=Li) may be prepared from the activated carboxylic acid derivative of the formula IX, as shown in the accompanied drawings, wherein R^2 is as described above, by adding the activated carboxylic acid derivative of formula IX , at an appropriate temperature, for example at about -70°C, to a solution of a strong base, such as lithium diisopropylamide or lithium hexamethyldisilazide. Other metal enolates of formula III may be prepared from the corresponding lithium enolate by addition of metal salts such as $MgBr_2$, $ZnCl_2$ or $Ti(OPr)_3Cl$.

Aldehyde of formula II may be prepared by methods known in the art, such as those described in *Synthesis*, 1994, 1294-1300 for the corresponding R enantiomer, using (S)- BINAP instead of (R)-BINAP for the asymmetric catalytic hydrogenation.

The hydrolysis of the diastereomeric mixture of trans-oxetan-2-ones of formula IV to remove the t-butyldimethylsilyl protecting group may be carried out in the presence of an acidic catalyst in a polar solvent to afford an oxetan-2-one of the formula I (SSS) and the other trans-diastereomer (SRR).

Examples of acidic catalyst include an acid such as, hydrofluoric acid and hydrochloric acid; a salt of a weak base such as, ammonium fluoride and pyridinium-4-toluenesulphonate; an acidic ion-exchange resin such as, Dowex 20® (E. Merck), or acidic silicagel (obtained by treatment of silicagel with methanolic hydrochloric acid).

Examples of polar solvents include alcohols such as methanol, ethanol and isopropanol; cyclic ethers, such as dioxane and tetrahydrofuran(THF); nitriles, such as acetonitrile; dipolar aprotic solvents such as dimethylformamide, dimethyl sulphoxide, sulpholane and N-methylpyrrolidone; esters such as ethyl acetate and isopropyl acetate; and mixtures thereof.

The hydrolysis may be carried out at a temperature range from about –20°C to about,120°C, or at a temperature range from about 0°C to about 60°C. In some particular examples it may be carried out at a temperature range from about 10°C to about 40°C.

The diastereomerically pure oxetan-2-one of the formula I is obtained from the diastereomeric mixture by crystallization from a suitable solvent(s). Examples of suitable solvents include aliphatic hydrocarbons, such as hexane, pentane, heptane, cyclohexane, and mixtures thereof. Mixtures of aliphatic hydrocarbons with aromatic hydrocarbons, such as toluene, and xylene; ethers, such as diisopropyl ether, dibutyl ether, diethyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran(THF); chlorinated hydrocarbons such as methylenedichloride and ethylenedichloride; esters such as ethyl acetate and isopropyl acetate; ketones such as acetone and methylisobutylketone (MIBK) may also be used.

The oxetan-2-one of formula I may be converted to a compound of formula V, by methods known in the art, such as those described in US 4983746; US 5175186; *Helv. Chim. Acta*, 1987, 53, 1218-1221; and *J. Org. Chem.* 1988, 53, 1218-1221 which are incorporated herein by reference.

In general, the acid anhydride of an acid of formula VI, or a mixed anhydride thereof, is used for esterification of the oxetan-2-one of formula I; followed by cleaving off the amino protecting group R^5 of the ester of formula VIII so obtained; and reacting with an alkanoylating agent which introduces the group R^4 to obtain the compound of formula V.

Alternatively, the compound of Formula V can be prepared by directly esteryfying the oxetan-2-one of formula I with an acid anhydride of an acid of formula VII, or a mixed anhydride thereof, wherein R^3 and R^4 are as defined in formula V. However, lower yields may be obtained with this process (*J. Org. Chem.* 1991, 56, 4716; Chem Comm. 1999, 17, 1743-1744).

The compounds of Formula V wherein R^1 is undecyl may also be prepared by hydrogenating a compound of formula V wherein R^1 is 2Z,5Z-undecadienyl.

Examples of amino protecting group R^5 include benzyloxycarbonyl and p-nitrobenzyloxycarbonyl.

The acid anhydrides may be obtained by reacting an acid of formula VI, or VII, with dicyclohexylcarbodiimide or N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide. The preparation of this acid anhydride may be carried out in a suitable solvent such as methylene chloride while cooling, for example to 0 to 5°C. The dicyclohexylurea byproduct is filtered off and the subsequent esterification can be carried out in a solvent such as dimethylformamide in the presence of dimethylaminopyridine at room temperature.

The mixed acid anhydride may be obtained by reacting an acid of formula VI, or VII, with a suitable acid halide, such as pivaloyl chloride in a solvent, such as dimethylformamide while cooling, for example to about -5 to 0°C, and the subsequent esterification can be carried out in the same solvent at the same temperature.

The cleavage of amino protecting group R^5 may be carried out by hydrogenation in a solvent, for example, ethers such as dioxane and tetrahydrofuran; chlorinated hydrocarbons such as methylenedichloride and ethylenedichloride; and esters such as ethyl acetate and isopropyl acetate in the presence of a hydrogenation catalyst such as palladium-on-carbon, at a temperature of about 10 to 75°C. The hydrogenation may be carried out at normal pressure, or at elevated pressure. In general, it may be carried out at a hydrogen pressure range from 1 to 2 atmospheres.

An undecadienyl group present in V is hydrogenated to the undecyl group during the hydrogenolytic cleavage of the amino protecting group.

The alkanoylating agent may be an acid anhydride, specifically formic acid anhydride or acetic acid anhydride; a mixed acid anhydride such as formic acid/acetic acid anhydride; or an acid halide, such as acetyl chloride. The alkanoylation may be carried out in a suitable solvent, for example, ethers such as dioxane and tetrahydrofuran; and chlorinated hydrocarbons such as methylenedichloride and ethylenedichloride at room temperature. A base such as triethylamine may be added in case an acid halide is used.

An improved process for preparing a compound of formula V is provided, which involves treating the oxetan-2-one of formula I directly with an acid of formula VI, and dicyclohexylcarbodiimide, followed by deprotection of the amino protecting group and alkanoylation as above.

The ester of formula VIII is thus obtained in a single step, wherein the acid anhydride of formula VI is formed *in situ* and simultaneously used up in esterification. The process may be performed in a suitable solvent, optionally in the presence of dimethylaminopyridine. Example of suitable solvents include chlorinated hydrocarbons such as methylenedichloride and ethylenedichloride; hydrocarbons such as hexane, cyclohexane, toluene, and xylene; ethers such as diethyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran(THF);dipolar aprotic solvents such as dimethylformamide and dimethylacetamide; esters such as ethyl acetate and isopropyl acetate; and mixtures thereof. The reaction may be carried out at a temperature range from about -20°C to about 40°C.

In the following section preferred embodiments are described by way of examples to illustrate the process. However, these are not intended in any way to limit the scope of the claims. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Procedure 1

Preparation of methyl (S)-3-(tert-butyldimethylsiloxy)tetradecanoate

A solution of methyl (S)-3-hydroxytetra decanoate (100 g, 0.387 mol) was added to dimethylformamide (150 ml), cooled to 5 to 10°C, and imidazole (66.2 g, 0.972 ml) in dimethylformamide (150 ml) was added, followed by the drop-wise addition of tert-butyldimethylsilyl chloride (87.0 g, 0.577 mol) in dimethylformamide (150ml). The mixture was then stirred for 8 to 10 hours at room temperature. The mixture was poured into water (5.0 l) with stirring and the product extracted into hexane (3 x 1.0 l). The combined organic layer was washed with saturated sodium chloride solution followed by water, dried and concentrated under reduced pressure to obtain the title compound as a residue (156 g).

Procedure 2

Preparation of (S)-3-(tert-butyldimethylsiloxy)tetradecanal

A solution of methyl-(S)-3-(tert-butyldimethylsiloxy)tertradecanoate (155 g) in toluene (600 ml) was cooled to –80°C. A solution of DIBAL-H (20% in toluene, 400 ml) was diluted with another 400 ml of toluene and added drop-wise at -80°C during 2 to 3 hours under stirring. The mixture was stirred at –80°C for 30 minutes. Methanol (50 ml) was added to the reaction at -70°C to -80°C. Further, saturated sodium chloride solution (400 ml) was added followed by hyflow (50 g) and sodium sulfate (25 g) at room temperature. The solid was filtered and washed with toluene (200 ml). The combined organic layer was washed with saturated sodium chloride solution (200 ml) followed by water (200 ml), dried over sodium sulfate, concentrate under reduce pressure to obtain the title compound as a residue (136 g).

EXAMPLE 1

Preparation of 3-hexyl-4[(2s)-2-tert-butyldimethylsiloxytridecyl] oxetan -2-one [(3S,4S) + (3R,4R)]

Lithium hexamethyldisilazide (20% THF, 400 ml) was cooled to –95°C and a solution of N-octanoylbenzotriazole (100 g in 350 ml THF) pre-cooled to –40°C was added at a rate sufficient to maintain the temperature at –95°C. After complete addition, the reaction mixture was stirred at –95°C for 30 minutes. The crude (S)-3-(tert-butyldimethylsiloxy)tetradecanal of procedure 2 above(135 g in 200 ml THF) was cooled to –50°C and then added to the lithium enolate at a rate sufficient to maintain the temperature at –95°C for 30 minutes and warmed to 0°C. Dilute hydrochloric acid (2N, 380 ml) was then added and the mixture stirred for 10 to 15 minutes. Hexane (500 ml) was then added, stirred for 15 minutes and the organic layer was separated. Aqueous layer was re-extracted with hexane (300 ml). The combined hexane layer was washed with saturated sodium chloride solution (200 ml) followed by water (200 ml) and concentrated under reduce pressure till a thick mass was obtained. Fresh hexane (600 ml) was added to the thick mass and stirred at room temperature for 1 hour. The solid that precipitated out (benzotriazole) was filtered off and washed with hexane. Combined hexane layer was concentrated under reduce pressure to get a thick residue, which was dissolved in ethyacetate: hexane (5: 95 v/v) and passed through silica gel bed to get the title diastereomeric mixture (150 g).

EXAMPLE 2

Preparation of (3S,4S)-3-hexyl-4[(2S)-2-hydroxy]oxetan-2-one

A solution of the diastereomeric oxetanone mixture obtained in example 1(150 g) in acetonitrile (600 ml) was cooled to 10 to 15°C. Aqueous hydrofluoric acid (40%, 15 ml) was added drop-wise and the reaction mixture was stirred for 10 hours at room temperature. The mixture was poured in water (3 l) and extracted with hexane (750 ml). The hexane layer was separated and the aqueous layer was re-extracted with hexane (250 ml). Combined hexane layer was washed with saturated sodium bicarbonate solution (300 ml), followed by washing with water. Hexane was distilled out under reduce pressure to obtain a thick residue (130 g) which was then stirred in hexane (450 ml) at 0°C. The precipitated solid was filtered and washed with cold hexane to get 58 g of the title compound.

EXAMPLE 3

Preparation of (S)-N-[(benzyloxy)carbonyl]leucine (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]dodecyl ester

A solution of (S)-N[(benzyloxy)carbonyl]leucine (200 g, 0.6214 mol) in toluene (100 ml), was cooled to –10 to 0°C. 1,3-Dicyclohexylcarbodimide (90 g, 0.436 mol) in toluene (300 ml) was slowly added to it, followed by the addition of the product from example 2 (100 g, 0.282 mol) and 4-(N, N-dimethylamino)pyridine (10 g). The reaction mixture was stirred for 1 hour at 0 to 10°C, the residual urea derivative was filtered off and the filter cake was washed with toluene (100 ml). Combined toluene filtrate was washed with aqueous hydrochloric acid, sodium bicorbonate and water. After carbon treatment of toluene layer and recovery of toluene, the product was recrystallized with hexane (100 ml), filtered, washed with hexane (200 ml) and dried to provide 150 g (yield: 89%) of the title compound.

EXAMPLE 4

Preparation of (S)-leucine (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester

A solution of the product from example 3 (100 g, 0.166 mol) in methanol (300 ml) was hydrogenated in the presence of 10% Pd/C (10 g, 50% moisture) at room temperature under hydrogen atmosphere (20 to 60 psi) for 2 hours. The title product was obtained after filtration and evaporation of methanol as a residual oil 80 g (purity: 90% by HPLC, yield: 93%).

EXAMPLE 5

Preparation of (S)-N-formylleucine (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]dodecyl ester(Orlistat)

To the solution of the product from example 4 (100 g, 0.214 mol) in dichloromethane (700 ml), formic acid / acetic anhydride reagent (245g, obtained by mixing 157.6g of formic acid in 87.4g of acetic anhydride) was added slowly at –5 to 5°C. The reaction was monitored by TLC (ethyacetate: hexane :: 30: 70 v/v, I_2). After completion of the reaction the reaction mixture was washed with water, sodium bicarbonate solution and brine, the dichloromethane was recovered completely. Orlistat (63.0 g) was obtained after recrystallization with n-pentane.
Assay: 99.4% by HPLC

WE CLAIM:

1. A process for preparing oxetan-2-one of formula I, wherein R^1 is undecyl or 2Z,5Z-undecadienyl, as shown in the accompanied drawings, comprising:
   a. reacting an aldehyde of formula II, as shown in the accompanied drawings, wherein R^1 is undecyl or 2Z,5Z-undecadienyl, with a metal enolate of formula III, wherein R^2 is selected from the group consisting of fluorine, substituted or unsubstituted aryloxy, arylsulfanyl and heteroaryl groups, and M is selected from the group of mono-, di-, tri- and tetravalent metal containing groups;
   b. hydrolyzing the resulting diastereomeric mixture of trans-oxetan-2-ones of formula IV, wherein R^1 is as defined above; and
   c. separating of the diastereomerically pure oxetan-2-ones of formula I by crystallization.

2. The process as claimed in claim 1 for the preparation of a compound of formula I, wherein R^1 is 1-benzotriazolyl and M is lithium.
3. The process as claimed in claim 1, wherein the reaction of the aldehyde of formula II with the metal enolate of formula III is performed in an ether solvent selected from the group consisting of diethyl ether, dibuyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran(THF).
4. The process as claimed in claim 1, wherein the reaction of the aldehyde of formula II with the metal enolate of formula III is carried out at a temperature range of from about -120°C to about -70°C.
5. The process as claimed in claim 1, wherein the hydrolysis of the diastereomeric trans-oxetan-2-one of formula IV is carried out in the presence of an acidic catalyst in a polar solvent.
6. The process as claimed in claim 5, wherein the acidic catalyst is selected from the group consisting of an acid, a salt of a weak base, an acidic ion-exchange resin and acidic silicagel.
7. The process as claimed in claim 6, wherein the acid is hydrofluoric acid or hydrochloric acid.
8. The process as claimed in claim 6, wherein the salt of a weak base is ammonium fluoride or pyridinium-4-toluenesulphonate.

9. The process as claimed in claim 5, wherein the polar solvent is selected from the group consisting of alcohols, cyclic ethers, nitriles, dipolar aprotic solvents, esters, and mixtures thereof.
10. The process as claimed in claim 9, wherein the alcohol is selected from the group consisting of methanol, ethanol and isopropanol.
11. The process as claimed in claim 9, wherein the cyclic ether is selected from the group consisting of dioxane and tetrahydrofuran(THF).
12. The process as claimed in claim 1, wherein the crystallization is performed in an aliphatic hydrocarbon solvent selected from the group consisting of hexane, pentane, heptane, cyclohexane, and mixtures thereof.
13. The process as claimed in claim 1, wherein an additional solvent selected from the group consisting of aromatic hydrocarbons, ethers, chlorinated hydrocarbons, esters, ketones and mixtures thereof is used.
14. The process as claimed in claim 1, further comprising converting oxetan-2-one of formula I, wherein R^1 is undecyl or 2Z,5Z-undecadienyl to a compound of formula V, as shown in the accompanied drawings, wherein R^1 is as defined above; R^3 is isobutyl or carbamoylmethyl ; and R^4 is formyl or acetyl.
15. The process as claimed in claim 14, wherein the conversion to compound of Formula V is achieved by esteryfying the oxetan-2-one of formula I with an acid anhydride of an acid of formula VI, as shown in the accompanied drawings, or a mixed anhydride thereof, wherein R^3 is as defined above, and R^5 is an amino protecting group; followed by cleaving off the amino protecting group R^5; and reacting with an alkanoylating agent to introduce the group R^4.
16. A process for preparing a compound of formula V, comprising treating an oxetan-2-one of formula I directly with an acid of formula VI, wherein R^3 and R^5 are as defined above, and dicyclohexylcarbodiimide; followed by cleaving off the amino protecting group R^5; and reacting with an alkanoylating agent to introduce the group R^4.
17. The process as claimed in claim 16, wherein the treatment of oxetan-2-one of formula I with the acid of formula VI is performed in a solvent selected from the group consisting of hydrocarbons, chlorinated hydrocarbons, ethers, esters, dipolar aprotic solvents, and mixtures thereof.
18. The process as claimed in claim 16, wherein the hydrocarbon is selected from the group consisting of hexane, cyclohexane, toluene, and xylene.

19. The process as claimed in claim 16, wherein the treatment of oxetan-2-one of formula I with the acid of formula VI is performed in the presence of dimethylaminopyridine.

20. The process as claimed in claim 16, wherein the treatment of oxetan-2-one of formula I with the acid of formula VI is performed at a temperature range from about -20°C to about 40°C.

21. The process as claimed in claim 15 or 16, wherein R^5 in the acid of formula VI is benzyloxycarbonyl or p-nitrobenzyloxycarbonyl.

22. The process as claimed in claim 15 or 16, wherein the alkanoylating agent is selected from the group consisting of an acid anhydride, a mixed acid anhydride, and an acid halide.

23. A process for preparing oxetan-2-one of formula I, as herein described and illustrated by the examples herein.

Dated this 8TH day of **JULY, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

0 0 0 0 DEL 0 3

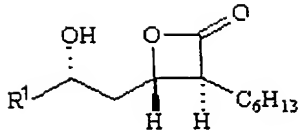
15 JUL 2003

Ranbaxy Laboratories Limited

No. of sheets = 09

Application No.

Sheet 01 of 09



FORMULA I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

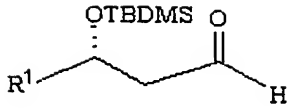
DEC 07
15 JUL 2003

Ranbaxy Laboratories Limited

No. of sheets = 09

Application No.

Sheet 02 of 09



FORMULA II

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

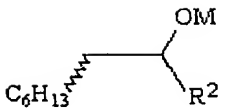
No. of sheets = 09

Application No.

Sheet 03 of 09

0900DEL07

15 JUL 2003



FORMULA III

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

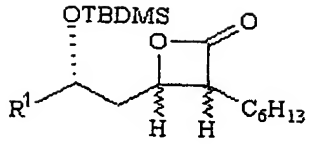
Ranbaxy Laboratories Limited

Application No.

No. of sheets = 09

Sheet 04 of 09

15 JUL 2003



FORMULA IV (SSS+SRR)

FINAL

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

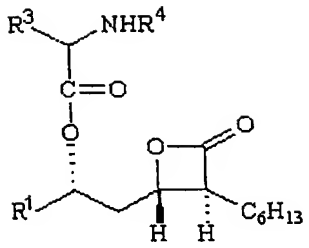
No. of sheets = 09

Application No.

Sheet 05 of 09

DEL

15 JUL 2003



FORMULA V

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

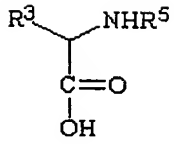
Application No.

No. of sheets = 09

Sheet 06 of 09

DEC 07

15 JUL 2003



FORMULA VI

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ORIGINAL

Ranbaxy Laboratories Limited

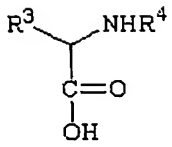
Application No.

No. of sheets = 09

Sheet 07 of 09

DEL 03

15 JUL 2005



FORMULA VII

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

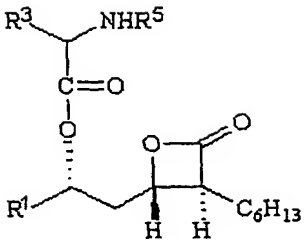
Ranbaxy Laboratories Limited

No. of sheets = 09

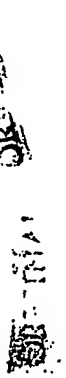
Application No.

Sheet 08 of 09

15 JUL 2003



FORMULA VIII



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

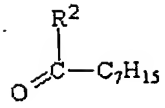
No. of sheets = 09

Application No.

Sheet 09 of 09

DEL 07

15 JUL 2003



FORMULA IX

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

09900 DEL 03

15 JUL 2003

ABSTRACT

The present invention relates to processes for the preparation of diastereomerically and enantiomerically pure oxetan-2-ones are provided. Further, processes for the preparation of enzyme inhibitors using the oxetan-2-ones are provided.

ORIGINAL

PCT/IB2004/002305

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